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Problem Behavior of Dementia Patients Predicts Low-Grade Hypercoagulability in Spousal Caregivers

Roland von Känel,[1,2] Brent T. Mausbach,[2] Joel E. Dimsdale,[2] Paul J. Mills,[2] Thomas L. Patterson,[2] Sonia Ancoli-Israel,[2] Michael G. Ziegler,[3] Susan K. Roepke,[2,4] Matthew Allison,[5] and Igor Grant[2]

[1]Department of General Internal Medicine, Division of Psychosomatic Medicine, Inselspital, Bern University Hospital and University of Bern, Switzerland.
[2]Department of Psychiatry, University of California, San Diego, La Jolla.
[3]Department of Medicine, University of California, San Diego, La Jolla.
[4]San Diego State University Joint Doctoral Program in Clinical Psychology, California.
[5]Department of Family and Preventive Medicine, University of California, San Diego, La Jolla.

Address correspondence to Roland von Känel, MD, Department of General Internal Medicine, Division of Psychosomatic Medicine, Inselspital, Bern University Hospital, CH-3010 Bern, Switzerland. Email: roland.vonkaenel@insel.ch

Background. Low-grade hypercoagulability might be one pathway to explain how the chronic stress of dementia caregiving increases cardiovascular disease risk, but the specific aspects of caregiver stress that elicit hypercoagulability are elusive. We hypothesized that dementia patients' problem behaviors and negative reactions of caregivers to these behaviors would relate to hypercoagulability in caregivers.

Methods. One hundred and eight participants (mean age 74 ± 8 years, 70% women) providing in-home care for their spouse with Alzheimer's disease were examined. Caregivers were interviewed about the number of 24 predefined patient problem behaviors in the previous week (range 0–24) and how upset or bothered they felt in response to these behaviors (total score 0–96). Von Willebrand factor, plasminogen activator inhibitor-1, and D-dimer were determined in plasma and standardized *z*-scores of their concentrations summed into a procoagulant index.

Results. Greater number of problem behaviors ($\Delta R^2 = 0.046$, $p = .014$) and negative reactions of caregivers to these behaviors ($\Delta R^2 = 0.044$, $p = .017$) were associated with greater procoagulant index after controlling for sociodemographic factors, major cardiovascular risk factors, health habits, and health problems. However, the number of and reaction to problem behaviors did not significantly predict procoagulant activity independent from each other. Post hoc analysis revealed a positive association between the number of problem behaviors and D-dimer ($p = .010$, $\Delta R^2 = 0.053$), even when controlling for negative reactions ($p = .033$, $\Delta R^2 = 0.036$). Caregiver reaction to problem behaviors was not significantly associated with any procoagulant factor individually.

Conclusion. Alzheimer patients' problem behavior and their negative appraisal by the caregiver may contribute to the chronic low-grade hypercoagulable state in dementia caregivers.

Key Words: Alzheimer's disease—Psychological stress—Caregiving—Blood coagulation—Biomarkers.

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THE chronic stress of providing care to a spouse with dementia has been associated with poor physical outcome, particularly cardiovascular disease (CVD) (1,2). Compared with individuals who are not caregivers, caregivers more frequently develop incident coronary heart disease (CHD) (3,4) and have a higher Framingham CHD risk score (5). Studies have identified specific aspects of caregiving stress contributing to increased CVD risk independent of a range of sociodemographic factors, classic CVD risk factors, and health status of the caregiver. After 1.5 years of follow-up, depressed mood and negative reactions of caregivers to problem behaviors from the demented spouse predicted CVD, including risk of myocardial infarction (MI) (6). Providing care for at least 9 h/d to a disabled or ill spouse increased risk of nonfatal MI plus CHD-related mortality in women during 4 years of follow-up (4). Similarly, psychological strain predicted all-cause mortality after a 4-year follow-up in elderly caregivers of a spouse with health-related impairment in daily functioning (7).

A hypercoagulable state referring to enhanced clotting (ie, excess fibrin formation) and/or reduced fibrinolysis (ie, diminished fibrin dissolution) plays a key role in atherosclerosis, the underlying process of CHD (8). Importantly, there exists a continuum between normal functioning of hemostasis, hemostatic abnormalities in chronic low-grade hypercoagulable states contributing to atherosclerosis progression,

and acute thrombosis of a coronary artery leading to MI (9). We previously provided evidence for the hypothesis that caregiver stress might contribute to CHD by eliciting chronic low-grade hypercoagulability. Compared with their noncaregiving counterparts, spousal Alzheimer's caregivers showed higher levels of procoagulant D-dimer (10) and lower levels of fibrinolysis (11). In addition, dementia severity of the care recipient was associated with resting D-dimer levels in caregivers (12), suggesting that there might be unique behavioral aspects of dementia caregiving stress contributing to hypercoagulability. To further elucidate, such factors might offer important avenues for tailored behavioral interventions to improve cardiovascular health in caregivers.

We hypothesized that the number of problem behaviors exhibited by a spouse suffering from Alzheimer's disease as well as negative reactions of the caregiver to these behaviors would be associated with low-grade hypercoagulability. The latter was determined through plasma levels of von Willebrand factor (VWF), plasminogen activator inhibitor (PAI)-1, and D-dimer, all of which exert key functions in hemostasis. Specifically, VWF mediates platelet adhesion to endothelial lesions and platelet aggregation (13). Elevated VWF also indicates endothelial dysfunction that contributes to systemic hypercoagulability (14). PAI-1 is the major inhibitor of fibrinolysis as it binds to and inactivates circulating profibrinolytic tissue–type plasminogen activator (15). D-dimer is a marker of fibrin turnover (ie, fibrin formation and degradation) with higher levels indicating greater overall activation of the coagulation system (16). VWF, PAI-1, and D-dimer were previously shown to predict increased risk of future CHD (15,17,18) and to be associated with different types of chronic psychosocial stress (19,20).

Similar to previous biobehavioral studies, we defined a procoagulant index as a composite of standardized *z*-scores of VWF, PAI-1, and D-dimer (21,22). This approach concurs with recent systems' biology research by integrating complex hemostatic processes into one biologic pathway of hypercoagulability (23); it additionally guards against spurious findings from multiple comparisons between several behavioral and coagulation measures (22).

Methods

Study Participants

All participants provided written consent to the study protocol, which was approved by the University of California, San Diego (UCSD) Institutional Review Board. For the present study, we analyzed cross-sectional data obtained at the study entry of the UCSD "Alzheimer's Caregiver Study" investigating effects of dementia caregiving stress on health. Out of 121 enrolled caregivers, 11 had missing coagulation data, 1 blood pressure (BP) data, and 1 information on years of caregiving. This yielded a sample of 108 caregivers with a complete data set for the present investigation allowing us to compute full linear regression approach. To be eligible, caregivers had to be 55 years or older, to provide primary care for a spouse with a physician-based diagnosis of Alzheimer's disease, and to dwell with their spouse in the community. Exclusion criteria were presence of any major illnesses (eg, cancer), severe hypertension (BP >200/120 mm Hg), and treatment with warfarin or steroids (which would affect coagulation activity). Therapy with platelet inhibitory agents (eg, aspirin) was not an exclusion criterion. Caregivers were recruited through referrals from the UCSD Alzheimer's Disease Research center, community support groups and agencies serving caregivers, local senior citizen health fairs, and referrals from other participants.

Measures

A research associate conducted an interview on demographic- and health-related variables in the participant's home. Participants additionally completed questionnaires on health behavior and psychosocial data and had their blood sampled for coagulation analysis.

Sociodemographic factors.—We collected information on age, gender, and duration of care (ie, date from when the diagnosis of Alzheimer's disease was made to the interview date).

Body mass index.—We asked participants for their weight and height to calculate the body mass index (BMI).

Blood lipids.—Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were assessed in serum by the Beckman Coulter LX20 PRO (Beckman Coulter Inc, Brea, CA). The LDL-C/HDL-C ratio was computed and used for statistical analysis.

Blood pressure.—By means of a noninvasive Microlife blood pressure monitor (Microlife Inc, Dunedin, FL), three BP measurements were collected over a 15-minute resting period; the average was computed and defined as the participant's mean resting BP. We used systolic BP because it confers higher CVD risk than diastolic BP in individuals more than 50 years of age (24).

Smoking status.—Because only one caregiver currently smoked, we categorized participants into ever-smokers (ie, former plus current smokers) versus never-smokers.

Alcohol consumption.—Participants were asked on how many days they had at least one alcoholic drink during the past 30 days. Answer categories were 0, 1–2, 3–5, 6–9, 10–19, 20–29, and 30 days.

Physical exercise.—Participants were given the Rapid Assessment of Physical Activity scale asking about how often they do light (eg, vacuum cleaning), moderate (eg, fast

walking), and strenuous (eg, jogging) exercise per week. For each of the three exercise intensity categories, frequency was rated applying score points: 0 (0 days), 1 (1 or 2 days), 2 (3 or 4 days), 3 (5 or 6 days), 4 (every day), yielding a total exercise score from 0 to 12 (25).

Number of health problems.—Participants were asked the question "Do you currently have or has a doctor told you that you have any of the following health problems?" and provided a list with 18 items (eg, arthritis, heart disease, problems with your kidneys). The number of positive items was summed to reflect medical comorbidity.

Depressive symptoms.—We used the short form of the Center for Epidemiological Studies-Depression scale (CESD-10) to assess the level of depressed mood (26). A cutoff score of 10 or more on the CESD-10 is equivalent to the established cutoff of 16 on the full CESD scale.

Problem behaviors—The Revised Memory and Behavior Problem Checklist was used to measure the number of endorsed behavioral problems by the care recipient as well as the negative caregiver reaction to these problem behaviors (27). Caregivers were asked whether their spouse manifested any of the 24 behavior problems (7 memory, 9 disruptive, and 8 depressive) during the past week. Typical items relate to whether the spouse loses or misplaces things, appears sad or depressed, or becomes aggressive to others verbally. If their spouse exhibited a problem behavior at least once during the past week, they were asked to rate on a 5-point Likert scale how bothered or upset they felt by each behavior (0 = "not at all", 4 = "extremely"). An upset score of 0 was assigned to problem behaviors, which were not present. We computed a total negative reaction score by adding all 24 upset scores (range 0–96).

Procoagulant measures.—In order to not interfere with caregiver daily routine, fasting state was not a prerequisite. Venous blood was drawn into plastic syringes containing 3.8% sodium citrate (9:1, v/v) with minimal tourniquet pressure. The first 2 mL of blood were discarded. Samples were centrifuged at 4°C for 10 minutes at less than 1,300*g*. Obtained plasma was immediately stored at −80°C until analyzed. Concentrations of VWF antigen, PAI-1 antigen, and D-dimer were determined in duplicates using enzyme-linked immunosorbent assays as per the manufacturer's instructions (Asserachrom; Stago, Asnières, France). Intra- and interassay coefficients of variation were less than 10% for all measures. We calculated a procoagulant index by adding standardized *z*-scores of VWF, PAI-1, and D-dimer dividing the sum by 3.

Statistical Analysis

Data were analyzed using PASW 18.0 statistical software package (SPSS Inc., Chicago, IL) with level of significance at $p < .05$ (two-tailed). Normality of data distribution was verified using the Kolmogorov–Smirnov test. To achieve a Gaussian distribution, VWF, PAI-1, and D-dimer values were logarithmically transformed (*z*-scores for the procoagulant index were calculated on log-transformed values). Data for years of caregiving, alcohol consumption, and exercise did not show a normal distribution; therefore, they were categorized for statistical analysis. Years of caregiving were categorized into less than 2 years, 2 or more years but less than 5 years, and 5 or more years. Given the cardiovascular benefits of light-to-moderate alcohol intake of at least one drink/week (28), alcohol consumption was categorized into consumption on 0–5 days versus 6–30 days in the previous 30 days. Exercise scores were categorized as 0–4 versus 5–12 based on a median split.

Pearson correlation coefficients were calculated to estimate the association between two variables. We employed hierarchical linear regression analysis, using forced entry, to test the main hypothesis that (a) the number of problem behaviors endorsed by the dementia patient and (b) the negative reaction of the caregiver to behavior problems would significantly be linked to procoagulant measures independent of covariates. In case of a significant relation between problem behavior variables and the procoagulant index (significance level: $p < .025$ with Bonferroni correction for two behavioral variables), we performed a post hoc analysis for each procoagulant measure. An additional set of analyses was performed to explore the relationship between individual types of problem behaviors and procoagulant measures. We controlled for gender, age, BMI, dyslipidemia (ie, LDL-C/HDL-C ratio), systolic BP, smoking, alcohol consumption, physical exercise, and depressive mood because all these may affect coagulation (19,29). Because there is medical comorbidity in an elderly population that was shown to increase dementia caregiver stress (30) and may also affect coagulation, we controlled for the number of health problems. The duration of exposure to caregiving stress might be expected to affect coagulation activity, and thus, we also controlled for years of caregiving.

Results

Characteristics of Study Participants

Table 1 shows the descriptive statistics of the 108 spousal Alzheimer's caregivers who participated in this study. The study sample were predominantly women. In terms of traditional CVD risk factors, 22.2% of caregivers were overweight (BMI ≥30 kg/m^2), 10.2% had LDL-C/HDL-C ratio greater than 3.3 (31), and 35.2% had systolic BP in the hypertensive range (≥140 mm Hg). Almost half of the caregivers were ever-smokers. Only six caregivers indicated no health problems and 39.8% had clinically depressed mood as per a CES-D score of 10 or more.

The number of all 24 possible problem behaviors ranged from 2 to 21 (memory: 0–7, disruptive: 0–8, and depressive: 0–8). The reaction score about how bothered or upset care

Table 1. Characteristics of 108 Alzheimer's Caregivers

Variable	*M* ± *SD*	*n* (%)
Age (y)	73.8 ± 8.3	
Gender		
Female		76 (70.4)
Male		32 (29.6)
Body mass index (kg/m^2)	26.5 ± 4.8	
Blood lipids		
LDL-C (mg/dL)	104.7 ± 35.4	
HDL-C (mg/dL)	51.7 ± 15.7	
LDL-C/HDL-C ratio	2.15 ± 0.83	
Systolic blood pressure (mm Hg)	134.6 ± 15.4	
Ever-smoker		
Yes		48 (44.4)
No		60 (55.6)
Alcohol consumption		
0–5 d/mo		59 (54.6)
6–30 d/mo		49 (45.4)
Exercise (score)		
0–4		55 (50.9)
5–12		53 (49.1)
Number of health problems	3.4 ± 1.9	
Depressive mood (score)	8.7 ± 5.8	
Years of caregiving		
<2 y		33 (30.6)
≥2 y, <5 y		41 (38.0)
≥5 y		34 (31.5)
Procoagulant index (*z*-score)	0.00 ± 0.62	
von Willebrand factor (%)	182 ± 113	
Plasminogen activator inhibitor-1 (ng/mL)	38.0 ± 30.5	
D-dimer (ng/mL)	792 ± 435	
Number of all problem behaviors	11.1 ± 4.0	
Number of memory-related problem behaviors	6.0 ± 1.4	
Number of disruptive problem behaviors	2.2 ± 1.8	
Number of depressive problem behaviors	2.8 ± 2.2	
Reaction to all problem behaviors (score)	14.1 ± 12.0	
Reaction to memory-related problem behaviors (score)	5.2 ± 4.8	
Reaction to disruptive problem behaviors (score)	4.1 ± 5.1	
Reaction to depressive problem behaviors (score)	4.8 ± 5.0	

Notes: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

givers were about all these problems ranged from 0 to 55 (memory: 0–23, disruptive: 0–23, and depressive 0–20). By definition, the average of the standardized procoagulant index was 0 (range: −1.83 to 1.23). There were significant positive relationships between the number of problem behaviors and reaction to those behaviors in terms of all ($r = .70$, $p < .001$), memory-related ($r = .29$, $p = .003$), disruptive ($r = .86$, $p < .001$), and depressive ($r = .80$, $p < .001$) problem behaviors.

Bivariate Associations With Coagulation Measures

Table 2 gives the correlation matrix between health characteristics and coagulation measures. Except for an inverse association between LDL-C/HDL-C ratio and D-dimer levels, all the significant correlations pointed in the expected direction. Specifically, higher procoagulant index was associated with greater age, higher BMI, reduced exercise level, and more health problems. Higher VWF was significantly associated with lower frequency of alcohol consumption, and higher PAI-1 showed relationships with higher BMI, higher LDL-C/HDL-C ratio, previous smoking, and lower level of exercise. Higher D-dimer was significantly associated with greater age and more health problems. Neither the number of all memory-related, disruptive, and depressive problem behaviors nor caregivers' reaction to the sum of those behaviors were significantly associated with any coagulation measure in the bivariate analysis (ie, when not taking into account covariates).

Multivariate Analysis of Procoagulant Activity

Procoagulant index.—Table 3 shows that the number of all memory-related, disruptive, and depressive problem behaviors as well as caregivers' reaction to the sum of those behaviors were significantly related to the procoagulant index independent of covariates (age, gender, BMI, LDL-C/HDL-C ratio, systolic BP, smoking, alcohol consumption, exercise, health problems, depressed mood, and years of caregiving). Greater age, female gender, and higher BMI were also individually related to greater procoagulant index. After controlling for all covariates, the number of all problem behaviors and reaction to those behaviors explained 4.6% ($\Delta R^2 = 0.046$, $p = .014$) and 4.4% ($\Delta R^2 = 0.044$, $p = .017$), respectively, of the variance in the procoagulant index. To determine the relative roles in procoagulant activity of the number of problem behaviors and caregivers' reaction to those behaviors, we computed an additional multivariate model that included both these variables. Neither the number of problem behaviors nor the reaction to those behaviors was revealed as a significant predictor of the procoagulant index.

Individual procoagulant factors.—Because of the significance of the omnibus test, we performed post hoc analyses by regressing the number of all problem behaviors and caregiver reaction to those behaviors in two separate models on VWF, PAI-1, and D-dimer levels. We computed an additional model that included the number of all problem behaviors and reaction of caregivers to those behaviors. All these analyses controlled for age, gender, BMI, LDL-C/HDL-C ratio, systolic BP, smoking, alcohol consumption, exercise, health problems, depressed mood, and years of caregiving.

von Willebrand factor.—The number of problem behaviors ($B = 0.011 \pm 0.009$, $p = .211$) as well as caregiver reaction to problem behaviors ($B = 0.004 \pm 0.003$, $p = .227$) were not significant predictors of VWF in separate models. Likewise, when entering the model together, neither the number of problem

Table 2. Bivariate Associations Between Health Characteristics and Coagulation Measures

Participant Characteristics	Procoagulant Index	von Willebrand Factor	Plasminogen Activator Inhibitor-1	D-Dimer
Age	0.24*	0.15	–0.06	0.36***
Gender	0.13	–0.04	0.11	0.17
Body mass index	0.24*	0.16	0.37***	–0.08
LDL-C/HDL-C ratio	0.02	0.06	0.20*	–0.23*
Systolic blood pressure	0.16	0.13	0.05	0.12
Ever smoking	0.10	–0.07	0.21*	0.06
Alcohol consumption	–0.18	–0.20*	–0.06	–0.08
Exercise	–0.27**	–0.16	–0.34***	–0.01
Health problems	0.23*	0.07	0.16	0.20*
Depression	0.03	0.01	–0.02	0.07
Years of caregiving	–0.15	–0.17	–0.02	–0.09
Number of all problem behaviors	0.13	0.05	0.05	0.15
Reaction to all problem behaviors	0.17	0.08	0.06	0.18

Notes: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Pearson correlation coefficients with significance level are given: *$p < .05$, **$p < .01$, ***$p < .001$.

behaviors ($B = 0.007 \pm 0.012$, $p = .557$) nor the reaction to those behaviors ($B = 0.002 \pm 0.004$, $p = .625$) were revealed as significant predictors of VWF. None of the covariates emerged as a significant predictor of VWF in any model.

Plasminogen activator inhibitor-1.—The number of problem behaviors ($B = 0.006 \pm 0.010$, $p = .562$) and reaction of caregivers to problem behaviors ($B = 0.005 \pm 0.003$, $p = .113$) did not predict PAI-1 levels in separate models. When entered together into the model, the number of problem behaviors ($B = -0.009 \pm 0.013$, $p = .501$) and reaction to those behaviors ($B = 0.008 \pm 0.005$, $p = .106$) also did not emerge as significant predictors of PAI-1. In all models, higher BMI ($p \leq .035$) and lower level of exercise ($p \leq .047$) were associated with higher PAI-1.

D-dimer.—The number of problem behaviors significantly predicted D-dimer levels ($B = 0.015 \pm 0.006$, $p = .010$; $\Delta R^2 = 0.053$) and that relationship maintained significance when reaction to problem behaviors was additionally entered into the model ($B = 0.017 \pm 0.008$, $p = .033$; $\Delta R^2 = 0.036$). Greater age ($p < .001$) and female gender ($p \leq .048$) emerged also as independent predictors of higher D-dimer in those models. The relationship between reaction to problem behaviors and D-dimer levels was not significant when entering the model individually ($B = 0.003 \pm 0.002$, $p = .135$) and when the number of problem behaviors was also taken into account ($B = -0.001 \pm 0.003$, $p = .735$).

Individual types of problem behaviors and procoagulant activity.—Table 4 suggests that memory-related as well as depressive problem behaviors were more reliably associated with procoagulant activity than disruptive ones, controlling for covariates (age, gender, BMI, LDL-C/HDL-C ratio, systolic BP, smoking, alcohol consumption, exercise, health problems, depressed mood, and years of caregiving). Specifically, greater

Table 3. Multivariate Model for Procoagulant Index Predicted by All Problem Behaviors

	Number of all Problem Behaviors			Reaction to all Problem Behaviors			Number of Plus Reaction to All Problem Behaviors		
Entered Variables	Unstandardized Coefficient *B*	*SE*	*p* Value	Unstandardized Coefficient *B*	*SE*	*p* Value	Unstandardized Coefficient *B*	*SE*	*p* Value
Age	0.022	0.008	.005	0.020	0.008	.011	0.021	0.008	.007
Gender	0.281	0.128	.030	0.244	0.127	.058	0.269	0.129	.040
Body mass index	0.030	0.014	.032	0.033	0.014	.020	0.032	0.014	.024
LDL-C/HDL-C ratio	–0.001	0.072	.986	0.002	0.072	.982	0.004	0.072	.952
Systolic blood pressure	0.007	0.004	.067	0.006	0.004	.130	0.007	0.004	.081
Ever smoking	–0.021	0.116	.854	0.013	0.116	.912	–0.008	0.117	.946
Alcohol consumption	–0.202	0.114	.080	–0.194	0.114	.091	–0.202	0.114	.079
Exercise	–0.109	0.125	.382	–0.130	0.124	.297	–0.113	0.125	.365
Health problems	0.014	0.034	.682	0.007	0.035	.846	0.010	0.035	.782
Depression	–0.008	0.010	.438	–0.014	0.011	.225	–0.013	0.011	.268
Years of caregiving	–0.097	0.069	.159	–0.087	0.069	.211	–0.089	0.069	.204
Number of all problem behaviors	0.038	0.015	.014	—	—	—	0.024	0.021	.253
Reaction to all problem behaviors	—	—	—	0.013	0.005	.017	0.007	0.007	.320
Explained variance of entire model	$R^2 = 0.293$, $F(12,95) = 3.27$, $p < .001$			$R^2 = 0.290$, $F(12,95) = 3.28$, $p < .001$			$R^2 = 0.300$, $F(13,94) = 3.10$, $p < .001$		

Notes: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
Coding for categorical variables: female gender =1; ever-smoker = 1; alcohol consumption 6 or more days per month = 1; exercise 5 or more times per week = 1; years of caregiving = 1 (<2 years), 2 (≥2 years, <5 years), 3 (≥5 years).

Table 4. Multivariate Relationships Between Individual Types of Problem Behaviors and Procoagulant Measures

Types of Problem Behavior	Procoagulant Index	von Willebrand Factor	Plasminogen Activator Inhibitor-1	D-Dimer
Memory				
Number (main)	0.085 ± 0.041*	0.022 ± 0.023	−0.007 ± 0.026	0.048 ± 0.015**
Reaction (main)	0.023 ± 0.013	0.013 ± 0.007	<0.001 ± 0.008	0.007 ± 0.005
Number (relative)	0.073 ± 0.042	0.014 ± 0.024	−0.007 ± 0.027	0.046 ± 0.016**
Reaction (relative)	0.017 ± 0.013	0.012 ± 0.008	<0.001 ± 0.008	0.003 ± 0.005
Disruptive				
Number (main)	0.043 ± 0.036	0.012 ± 0.020	0.005 ± 0.022	0.019 ± 0.014
Reaction (main)	0.019 ± 0.012	0.003 ± 0.007	0.011 ± 0.007	0.005 ± 0.005
Number (relative)	−0.016 ± 0.068	0.017 ± 0.038	−0.078 ± 0.040	0.025 ± 0.026
Reaction (relative)	0.024 ± 0.023	−0.002 ± 0.013	0.033 ± 0.014*	−0.003 ± 0.009
Depressive				
Number (main)	0.058 ± 0.028*	0.018 ± 0.016	0.018 ± 0.017	0.017 ± 0.011
Reaction (main)	0.027 ± 0.012*	0.005 ± 0.007	0.016 ± 0.018*	0.006 ± 0.005
Number (relative)	0.027 ± 0.047	0.028 ± 0.027	−0.033 ± 0.029	0.019 ± 0.018
Reaction (relative)	0.017 ± 0.021	−0.006 ± 0.012	0.028 ± 0.013*	−0.001 ± 0.008

Unstandardized coefficient $B \pm SE$ are given: *$p < .05$, **$p < .01$. Main = main effect of number of problem behaviors and reaction to behaviors in separate models; relative = relative effect when entering number of problem behaviors and reaction to behaviors together.

number of memory-related problem behaviors was associated with greater procoagulant index ($p = .043$) and greater D-dimer levels ($p = .002$), the latter even after additional controlling for reaction to memory-related problem behaviors ($p = .005$). Moreover, greater number ($p = .038$) of and reaction ($p = .031$) to depressive problem behaviors were both significantly associated with greater procoagulant index in separate models but no longer so when entering the model together. In contrast, greater reaction to depressive problem behaviors predicted greater PAI-1 level with ($p = .028$) and without ($p = .031$) additional controlling for the number of depressive problem behaviors. Greater reaction to disruptive problem behaviors was associated with greater PAI-1 level after controlling for the number of those behaviors ($p = .019$).

Discussion

This study aimed to elucidate the specific aspects of caregiver stress that might be related to the chronic low-grade hypercoagulable state. We found that the total number of all memory-related, disruptive, and depressive problem behaviors exhibited by the care recipient with Alzheimer's disease was positively associated with a procoagulant index in the caregiver. In addition, the more bothered or upset the caregiver felt about their spouses' behavior problems, the higher was their procoagulant index. Consistent with the literature, greater age, female gender, and higher BMI emerged as independent predictors of higher procoagulant index. Those relationships might explain why the number of and reaction to all problem behaviors was unrelated to hypercoagulability in the univariate analysis but were revealed to independently predict hypercoagulability when making adjustments for correlates of hemostatic activity. Memory-related and depressive problem behaviors seemed more reliably related to procoagulant measures than disruptive behavior problems, although this observation needs replication.

We found that the individual associations of the number of and reaction to all problem behaviors with the procoagulant index were not independent of each other. However, both variables correlated substantially with each other such that much of their individual effects were partialled out statistically. In contrast, some relationships between individual types of problem behaviors and D-dimer and PAI-1 (but not VWF) were significant, even when taking into account joint effects of the number of and reaction to behavior problems. A parsimonious interpretation of these findings is that the mere count of dementia patients' problem behaviors and their negative appraisal by the caregiver predict procoagulant activity equally strongly.

Behavior problems associated with dementia, such as aggressive outbursts, troubles remembering events, and engagement in potentially dangerous activities, are among the most challenging stressors caregivers can face. Patient problem behaviors contribute significantly to psychiatric and physical morbidity in caregivers (32) as well as to home health aide use (33) and placement of the dementia patient in a nursing home (34). Our study suggests that patient problem behaviors might additionally affect cardiovascular health through kindling hypercoagulability. The measures included in our procoagulant index were predictive of atherosclerotic CVD (15,17,18) for which caregivers are at increased risk (3–6). D-dimer was also related to the number of all problem behaviors independent of covariates in post hoc analysis. Meta analysis has shown that elevated D-dimer predicts incident CHD risk independent of classic CVD risk factors (18) and recurrent coronary events in post-MI patients (35). It is noteworthy that D-dimer was stronger related to the number of all problem behaviors than were VWF and PAI-1. We previously showed in other samples of Alzheimer's caregivers that D-dimer levels were higher in caregivers than in noncaregiving controls (10), related to dementia severity of the spouse (12) and to noncaregiving-related negative life

events (36). In caregivers with no transition in the caregiving situation, D-dimer levels steadily increased over 5 years but began to significantly decline in the group with a transition at 6 months after bereavement or placement of the spouse (37). It follows from this research that, likely due to its value in indicating overall coagulation activation and its comparatively long half-life of up to 48 hours (17), D-dimer is a suitable biomarker of cardiovascular health related to the chronic stress of caregiving (21). There are several possible mechanisms through which patient problem behaviors might contribute to hypercoagulability in dementia caregivers, including sympathetic nervous system activation, poor sleep, and emotional arousal (38,39). Poor life style, however, seems a less probable reason because we controlled for smoking, alcohol intake, and exercise habits.

Our findings might have clinical implications given that, for instance, negative appraisal of problem behaviors was previously associated with time to CVD diagnosis in caregivers (6). Multimodal behavioral interventions, targeting cognitive appraisal, social support and education, reduce negative reactions of the caregiver to the patient problem behaviors with lasting effects (40,41). Likewise, reducing problem behaviors through training dementia patients in the use of aids to compensate for cognitive decline improve caregivers' quality of life (42), and occupational therapy sessions to help dementia caregivers modify the environment to support daily function of the patient reduces caregiver burden (43). It would be worthwhile to investigate whether such interventions might favorably affect the hypercoagulable state to ultimately mitigate dementia caregivers' CVD risk.

Our study has several limitations inherent to its cross-sectional design and to studies on physical outcomes in elderly patients with comorbidity and medical treatments that may potentially affect physiology. We adjusted for a range of predefined and common confounders of hemostasis measures, but we were unable to take into account separate effects of comorbid illnesses, such as, for instance, arthritis and heart diseases. This would have resulted in overadjusted and hence unstable models. Oral anticoagulants and steroids were exclusion criteria, but a range of other medications may potentially affect coagulation. Because such confounders would be assumed to further dilute the relationship between behavior problems and coagulation, this does not necessarily discount our findings. The direction of the relationship between problem behaviors and hypercoagulability remains unknown. However, on the one hand, it seems unlikely that a low-grade hypercoagulable state would affect a caregiver in a way that significantly affects the care recipient's behavior. On the other, hypercoagulability has been associated with cognitive impairment in individuals with subclinical atherosclerosis (44). Cognitive deficits might contribute to dysfunctional coping strategies making caregivers more vulnerable to react stressfully to a challenging environment. Problem behaviors explained between 4% and 5% of the variance in the procoagulant index. Whether this amount is clinically relevant is unclear. However, age, gender, and BMI explained a similar amount of that variance (ie, between 4% and 6%; analysis not shown). The inclusion of additional coagulation measures into our composite index, such as, for example, fibrinogen, might have increased the explained variance.

Taken together, dementia patients' problem behavior and their negative appraisal by the caregiver appear to contribute to the low-grade hypercoagulable state in Alzheimer's caregivers. This relationship might help explain the increased CVD risk in caregivers.

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